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(54) Title of the invention: METHOD FOR OPTICAL RESOLUTION OF RACEMIC GOSSYPOL

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SPECIFICATION

1. TITLE OF THE INVENTION

Method for optical resolution of racemic gossypol

2. SCOPE OF PATENT CLAIMS

1. A method for optical resolution of racemic gossypol characterized in that racemic gossypol is reacted with (−)-phenylalaninol in solvent, and the resultant diastereomer salts are separated by liquid chromatography.

2. A method for optical resolution of racemic gossypol as set forth in Claim 1 wherein said solvent is methanol.

3. DETAILED DESCRIPTION OF THE INVENTION

(FIELD OF INDUSTRIAL APPLICATION)

The present invention relates to a method for optical resolution of racemic gossypol, more specifically, a method for optical resolution of racemic gossypol whereby (+) (or −)-gossypol can be simply separated at high purity and high yield from racemic gossypol.

(PRIOR ART)

According to *Chemistry in Britain*, November 1984, page 970, it is known that gossypol contained in the meat of cottonseed and the like has (+) and (−) optical isomers. Furthermore, the gossypol obtained from one species of cotton, *Thespesia populnea*, is only (+) gossypol, but no species which produce only (−)-gossypol have been found.

This gossypol is known to have a sperm suppressant effect, but has been confirmed to produce side effects.

Namely, in animal experiments on hamsters, (±)-gossypol, which is the racemic form of gossypol, had a sperm suppressant effect, but caused anorexia as a side effect. On the other hand, (+)-gossypol alone did not produce this sort of sperm suppressant effect, while (−)-gossypol used alone had a marked sperm suppressant effect and no side effects, with the hamsters exhibiting body weight gain.

Furthermore, since the sperm suppressant effect has common points with an anticancer effect, (−)-gossypol is also promising as an anticancer drug.

In particular, it may be possible to further improve these effects for instance by introducing functional groups into (−)-gossypol.

(PROBLEM TO BE SOLVED BY THE INVENTION)

Thus, the efficient separation of racemic (±)-gossypol into (+)-gossypol and (−)-gossypol has been desired, but no methods that separate (+ or −) gossypol in a simple fashion at high purity and high yield have been achieved to date.

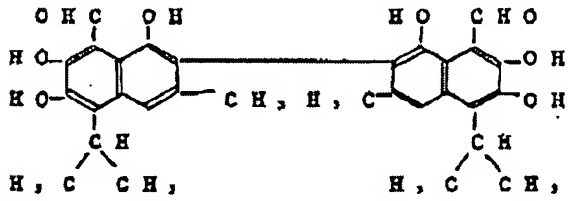
The present invention was made from this standpoint, its objective being to provide a method for optical resolution of racemic gossypol which allows (+ or −) gossypol to be obtained at high purity, high yield and in a simple fashion from racemic gossypol.

(MEANS OF SOLVING THE PROBLEM)

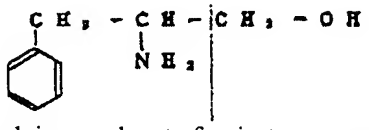
The aforementioned objective of the present invention is achieved by the following optical resolution method using (−)-phenylalaninol.

Namely, the present invention is a method for optical resolution of racemic gossypol, characterized in that racemic gossypol is reacted with (−)-phenylalaninol in solvent, and the resultant diastereomer salts are separated by liquid chromatography.

In the present invention, first, the racemic (±)-gossypol ($C_{30}H_{30}O_6$), having the following structural formula



and (−)-phenylalaninol, having the following structural formula,



are reacted in a solvent, for instance methanol, to produce diastereomer salts, which are a Schiff base. The resultant mixture of diastereomer isomers comprises (+)-gossypol/(−)-phenylalaninol and (−)-gossypol/(−)-phenylalaninol.

This mixture is separated into (+)-gossypol/(−)-phenylalaninol and (−)-gossypol/(−)-phenylalaninol using liquid chromatography. For this liquid chromatography, one can for instance use a reverse phase filler such as ODS or C-8 as the filler, and an alcohol-water mixed solution such as methanol-water or ethanol-water as the eluent. The mixing ratio of this alcohol-water mixture can be selected as desired.

The (+)-gossypol/(−)-phenylalaninol and (−)-gossypol/(−)-phenylalaninol obtained in this manner are dissolved in a mixed solution of dimethoxyethane and water mixed for example at a mixing volume ratio of 80:20, and are heated and hydrolyzed in the presence of a small amount of concentrated sulfuric acid.

The decomposition products are separated and purified by liquid chromatography to obtain (−)-gossypol and (+)-gossypol. For this liquid chromatography, one can also for instance use a reverse phase filler such as ODS or C-8 as the filler and a mixed solution of alcohol and water, such as methanol-water or ethanol-water, mixed at any desired ratio, as the eluent.

(EXAMPLE OF EMBODIMENT)

The present invention is described more specifically below based on an example of embodiment.

Example of embodiment

1000 mg (1.930 mmole) of (±)-gossypol, which is the racemic form of gossypol, and 706 mg (4.675 mmole) of (−)-phenylalaninol were dissolved in 30 ml methanol and stirred for 10 hours at room temperature (approximately 20°C), after which the methanol was distilled off under reduced pressure, and the resultant reaction product was separated using liquid chromatography under the following conditions.

(Separation conditions)

Column: Glass column, 45∅ × 490 mm, made by Sibata Scientific

Filler: Develosil ODS 30-50, made by Nomura Chemical

Eluent: Methanol-water = 95:5 (volume ratio)

Flow rate: 7.0 ml/min

1 fraction: 24.5 ml

As a result, 649 mg (yield: 42.9%) of (−)-gossypol/(−)-phenylalaninol was obtained from fractions 12 through 17, and 640 mg (yield 42.3%) of (+)-gossypol/(−)-phenylalaninol was obtained from fractions 21 through 32.

Next, a mixture of 225 mg of the obtained (−)-gossypol/(−)-phenylalaninol, 10 ml 80% dimethoxyethane solution and 10 drops of C-H_2SO_4 was heated and stirred for 3 hours at 60°C under a nitrogen atmosphere. After cooling, 50 ml of dichloromethane (CH_2Cl_2) was added thereto, washing first with water and then with saturated saline solution and then drying on sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure, and the resulting concentrate was separated using liquid chromatography under the following conditions.

(Separation conditions)

Column: Glass column, 24∅ × 360 mm, made by Sibata Scientific

Filler: Develosil ODS 30-50, made by Nomura Chemical

Eluent: Methanol-water = 90:10 (volume ratio)

Flow rate: 1.0 ml/min

1 fraction: 7.0 ml

As a result, 97 mg of (−)-gossypol was obtained (yield: 65.5%). Furthermore, it had the specific rotation $[\alpha]_D = -432°$ (C = 1.99, benzene).

The same separation as above was performed for (+)-gossypol/(−)-phenylalaninol.

Namely, a mixture of 200 mg of (+)-gossypol/(−)-phenylalaninol, 10 ml of 80% dimethoxyethane solution and 10 drops of C-H_2SO_4 was separated in the same manner as described above.

As a result, 82 mg of (+)-gossypol was obtained (yield: 62.1%). Furthermore, it had the specific rotation $[\alpha]_D = +416°$ (C = 1.84, benzene).

(EFFECT OF THE INVENTION)

As described above, the optical resolution method of the present invention allows (+ or −)-gossypol to be obtained from racemic gossypol at high purity, high yield and in a simple fashion.

The (+ or −)-gossypol obtained in this manner, especially the (−)-gossypol, has a sperm suppressant effect and is expected to have an anticancer effect with a high possibility of increasing these effects through the introduction of functional groups, making the optical resolution method of the present invention applicable in fields such as medicine and pharmaceutics.

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